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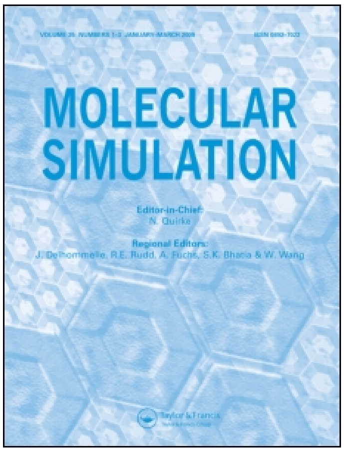

Molecular Simulation
Publication details, including instructions for authors and subscription information:
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To cite this Article Donnamaria, M. C. , Marañon, J. , Howard, E. I. , Fantoni, A. and Grigera, J. R.(1996) 'The Influence of Charge Calculation on Molecular Dynamics Simulation of Adenine in Water', Molecular Simulation, 18: 1, 101 — 113
To link to this Article: DOI: 10.1080/08927029608022356
URL: http://dx.doi.org/10.1080/08927029608022356

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Molecular Simulation, 1996, Vol. 18, pp. 101–113
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THE INFLUENCE OF CHARGE CALCULATION ON MOLECULAR DYNAMICS SIMULATION OF ADENINE IN WATER

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(Received September 1995: accepted March 1996)

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Molecular dynamics simulations of an aqueous solution of adenine have been performed using different methods of charge calculation to evaluate the influence of the values of the atomic charges on the dynamical results and to incorporate new information about the interaction between adenine and water. Four sets of partial charges where computed using *ab-initio* methods. In all cases the hydration properties of adenine were similar. These results support the view that the simulations by molecular dynamics, at least for the regime of infinite dilution, are not sensitive with respect to the different sets of partial charges used. A net hydrophobic behavior of the adenine molecule, on the water was observed.

Keywords: Charge calculation; molecular dynamics simulation; adenine hydration.

1. INTRODUCTION

Adenine is one of the smaller nucleic acid bases-whose staking structure yields the DNA conformation. Through the sequence of the nucleic acid bases the genetic information is coded and saved. The interest in studying the structural and electronic aspects of a biological molecule is because such aspects are intrinsically correlated with the molecule's biochemical activity [1].

Molecular Dynamics Simulation (MD) is a powerful technique for exploring many body systems, including carbohydrate [2–7] and protein [8,9] properties in solution and, therefore, such techniques may help provide a better understanding of the effect of adenine in water.

There are interesting quantum mechanical studies of the monohydration scheme of the adenine base of the nucleic acids [10–12]. With the SCF-LCAO-MO approximation [10], it was possible to search the interaction of adenine and the water molecule in more than 2000 positions; while with *ab initio wave functions* and isopotentials maps of the acid nucleic basis [11] was determined the preferred protonation sites of adenine compared to its corelative base: guanine. Furthermore, using the *overlap multipole procedure* [12] was resolved the hydration scheme of the adenine (among the other bases) leading to a representation of its first hydration shell.

One of the major problems in the use of MD is that some crucial data, as for instance molecular charge distribution can only be obtained through *ad hoc* calculations for a defined molecular conformation [3–6]. Furthermore, the absence of a general method for such a determination worsens the situation.

This paper deals with the simulation by molecular dynamics of adenine in aqueous solution in order to give a better understanding of the contribution of the influence of the values of the atomic partial charges to the dynamical results and to incorporate new information about the nucleic base adenine in its interaction with water.

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2. MODEL

In the model used, normal adenine was kept rigid in a planar conformation (as a common assumption) by applying improper torsion potentials that avoid transitions among other possible conformations. The hydrogen atoms were explicitly included. Particular geometry of carbon and nitrogen atoms were maintained also using improper torsion potentials. Bond lengths were kept rigid and bond angles treated as having harmonic potentials, using the values given by Brown *et al.* [13]. There were not applied torsion potentials on the NH_2 group, (amino group). The conformation is determined through the dihedrals only by the atom-atom interaction and solvent effects. It was adopted this approach since the inclusion of a predefined torsional potential [4,14,15]. will produce a bias in the calculated conformations

Force field parameters were used as given in GROMOS package (Biomos N.V., Groningen-Zurich). Hydrogen atoms only interact through their coulombic interaction. Four charge sets were used. The charges were computed with the Gaussian 92 (16) usig the 3-21 G* basis.

In the first set, DM1, the charges were obtained by Mulliken population analysis. In the second set, DM2, the net charges were obtained using the option of electrostatic potential calculation, *i.e.* a certain number of shell of points are selected in the space around the solute molecule. At these points the electrostatic potential is evaluated. AZ-matrix procedure is used to input an initial partial charge model in which the charges or alternatively, their location can be varied subject of some constrains on the charges and the partial charge dipole moment or quadrupole moment component of the molecule. Then the calculated potential is fitted to the one calculated by quantum mechanics (Mulliken population analysis) in order to obtain the final net atomic charges. The third set, DM3, consists of net charges obtained by Mulliken population analysis in the presence of solvent incorporating through the Onsager model (17–18) using a dielectric constant for the solvent of 10.7. Finally, the fourth set, DM4, the solvation effect is incorporated within the electrostatic calculation.

Figure 1 shows a scheme of the model and Table I the atomic partial charges.

Water was modeled using the SPC/E model [17]. It consists in a negative charge in oxygen location and repulsion-attraction potential of Lenard-Jones 12-6 type. Two positive charges are located at hydrogen position. The OH distance is kept at 0.1 nm and HOH angle at 109, 47°.

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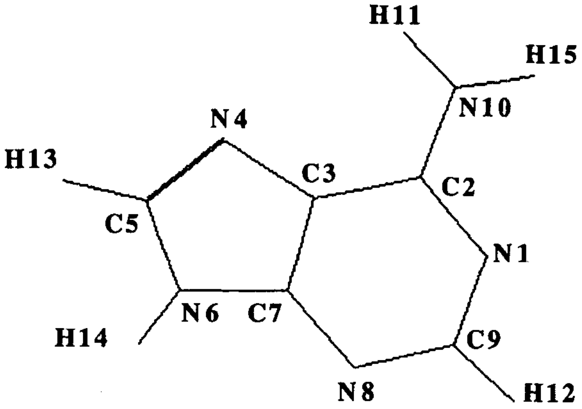

FIGURE 1 Scheme of adenine molecule.

TABLE I Atomic partial charges for adenine using in the simulations

Atom	*Charge-Set1*	*Charge-Set2*	*Charge-Set3*	*Charge-Set4*
N1	−0.7988	−0.8451	−0.8049	−0.8575
C2	0.8683	0.8324	0.8649	0.8472
C3	0.0685	0.0585	0.0705	−0.0668
N4	−0.6758	−0.6075	−0.6750	−0.6104
C5	0.3941	0.3145	0.3972	0.3316
N6	−0.9792	−0.6933	−0.9787	−0.7169
C7	0.8295	0.7527	0.8301	0.7777
N8	−0.7586	−0.8361	−0.7571	−0.8414
C9	0.3510	0.5971	0.3484	0.5915
N10	−0.9030	−0.2858	−0.9727	−0.9986
H11	0.3753	0.4291	0.3797	0.4351
H12	0.2337	0.0807	0.2522	0.0741
H13	0.2790	0.1995	0.2916	0.1518
H14	0.3886	0.4370	0.3919	0.4460
H15	0.3674	0.4378	0.3613	0.4366

3. METHOD

Molecular Dynamics simulations were run using the GROMOS package in a HP 710 Series Computer. Results were analyzed in a 486 personal computer. All runs were done at constant pressure and constant temperature, keeping them at 1.013 10^5 Pa and 300 K, respectively. Integration time step was 0.001 ps. Simulations were run for 200 ps after the equilibrium was reached. The criteria for equilibrium were the stability of box length and potential energy. One adenine molecule was located in a cubic box of a box length of 1.999 nm surrounded by 208 molecules of water.

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4. RESULTS AND DISCUSSION

4.1. Mobility

The libration of the amino group was taken as a measurement of the mobility of adenine. One of the most important features of the present model is the absence of an explicit torsional potential, which could bias the results. In this description such movements become only from the mutual atom interaction. Figure 2 shows the mobility of the amino dihedral angle (N1-C2-N10-H15) during the 200 ps. of spanned time for the four cases simulated.

The apparent very fast movements that are seen in Figures 2a and 2b are consequences of the discontinuity of the plotting at the end of the circular movements. There are only fluctuations around 0° (360°). We see that in the first two cases (DM1, DM2) the dihedral angle goes to a relative stable value around 0° (360°). For DM3 (Fig. 2c) the hydrogen pair group is more mobile, while for the last case (DM4-Fig. 2d) the dihedral value is also stabilized around 0° (360°).

This tendency to adopt an equilibrium state in which the fluctuations are nearly restricted to small values is consistent with the nucleic base pairing restrictions when the bases join to form the adenine-thymine base pair.

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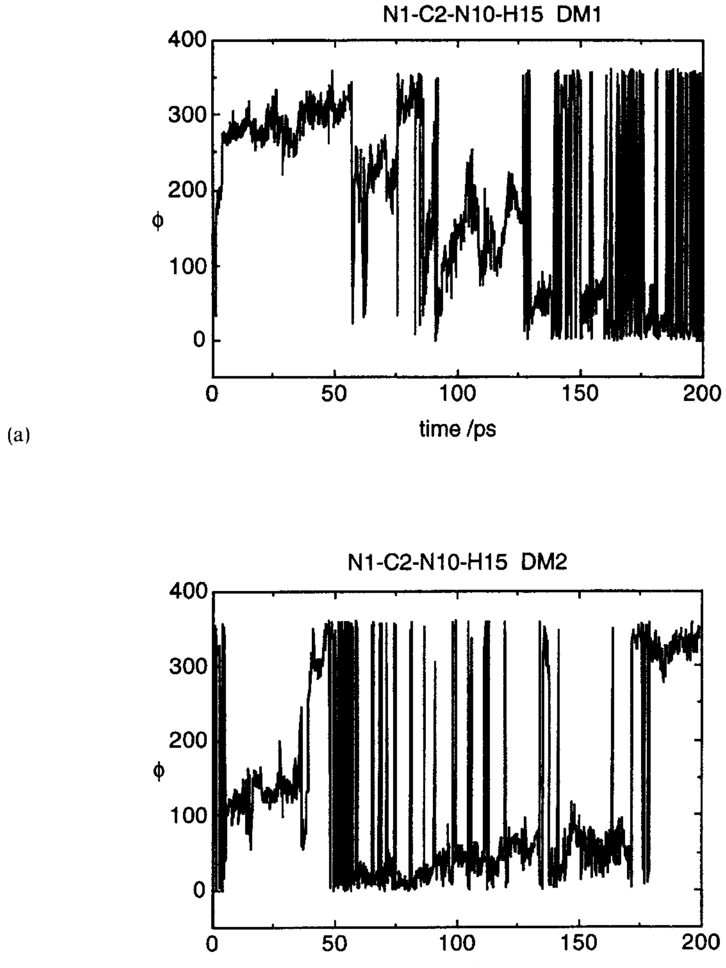

FIGURE 2 Trajectories of the amino dihedral angle (N1-C2-N10-H15) during the 200 ps. of spanned time for the four charge sets simulated. a) DM1, b) DM2, c) DM3, d) DM4.

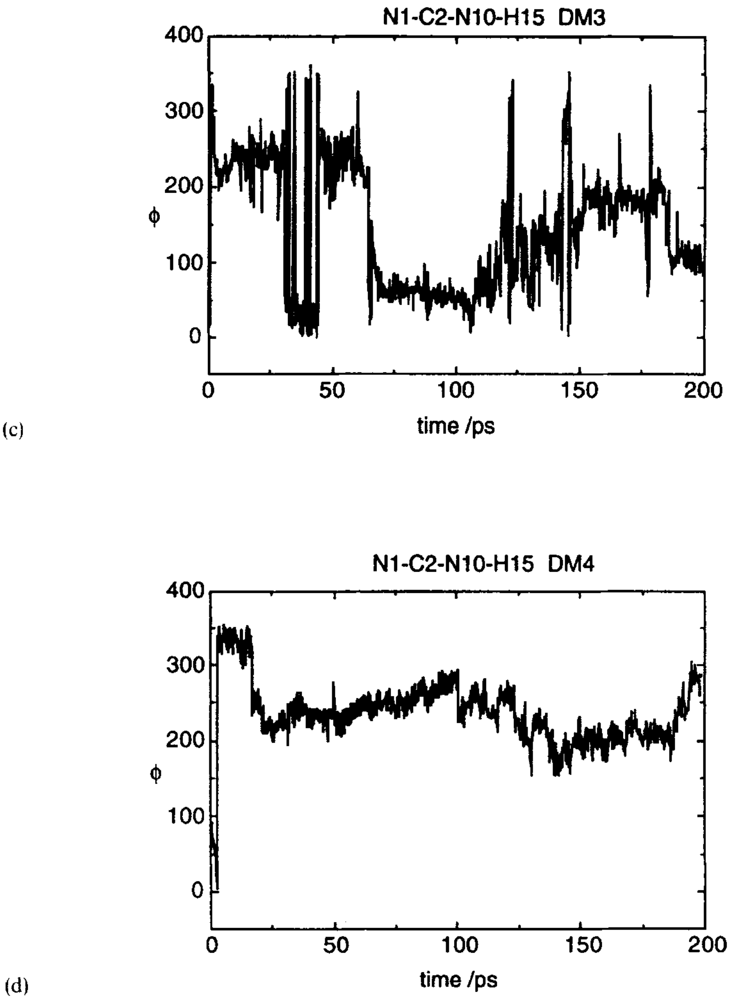

FIGURE 2 *Continued.*

4.2. Water Diffusion Coefficient

To evaluate the effect of adenine in the dynamics properties of water, we have computed the water-water diffusion coefficient from the atomic mean square displacement [18]

$$D = \lim_{t \to \infty} \frac{1}{6t} \frac{1}{n} \sum_{n} [x(0) - x(t)]^2 \qquad [1]$$

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Thus the diffusion coefficient will be proportional to the slope of the line of the mean square displacement $\langle \Delta x^2 \rangle = 1/n\Sigma_n[x(0) - x(t)]^2$ *versus* time, after the system reaches the diffusive regime. The simulated water diffusion coefficient in aqueous adenine solution takes for each case the following values $D_{A1} = 0.613 \times 10^{-5}\mathrm{cm}^2\mathrm{s}^{-1}$, $D_{A2} = 0.518 \times 10^{-5}\mathrm{cm}^2\mathrm{s}^{-1}$, $D_{A3} = 0.505 \times 10^{-5}\mathrm{cm}^2\mathrm{s}^{-1}$, $D_{A4} = 0.727 \times 10^{-5}\mathrm{cm}^2\mathrm{s}^{-1}$, while for pure SPC/E water $D_W = 2.211 \times 10^{-5}\mathrm{cm}^2\mathrm{s}^{-1}$.

Figure 3 displays comparatively the MSD values for pure water and for water-adenine for DM4 charge set. The runs with the others charge sets give similar values. It comes apparent that the water molecules movement is slowed down by the presence of the adenine, when compare with a pure SPC/E water.

4.3. Hydration

For each system the hydration properties have been studied through the radial distribution functions of water around each atom of adenine and their angular distribution function. Also hydrogen bond statistical was performed.

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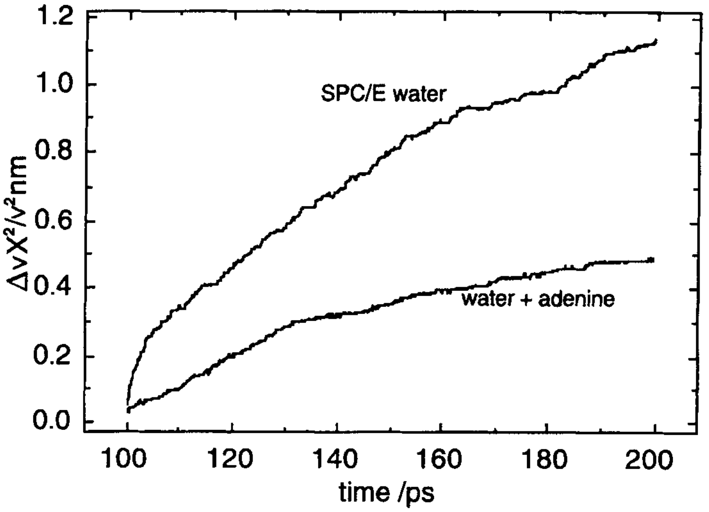

FIGURE 3 Mean square desplacement of water plotted against time for SPC/E water in the simulation of pure water and adenine solution.

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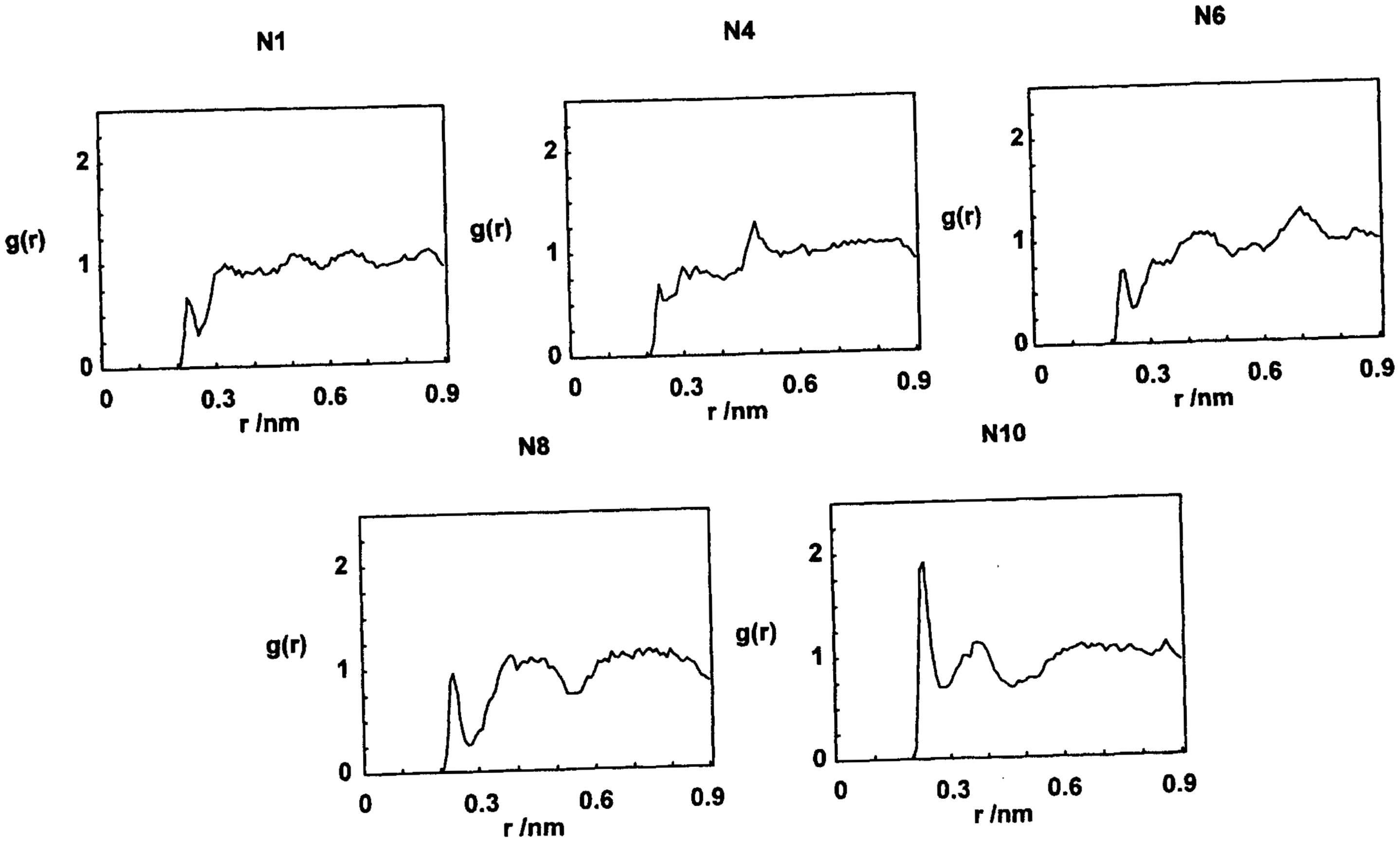

FIGURE 4 Radial distribution functions of water around nitrogen atoms of adenine.

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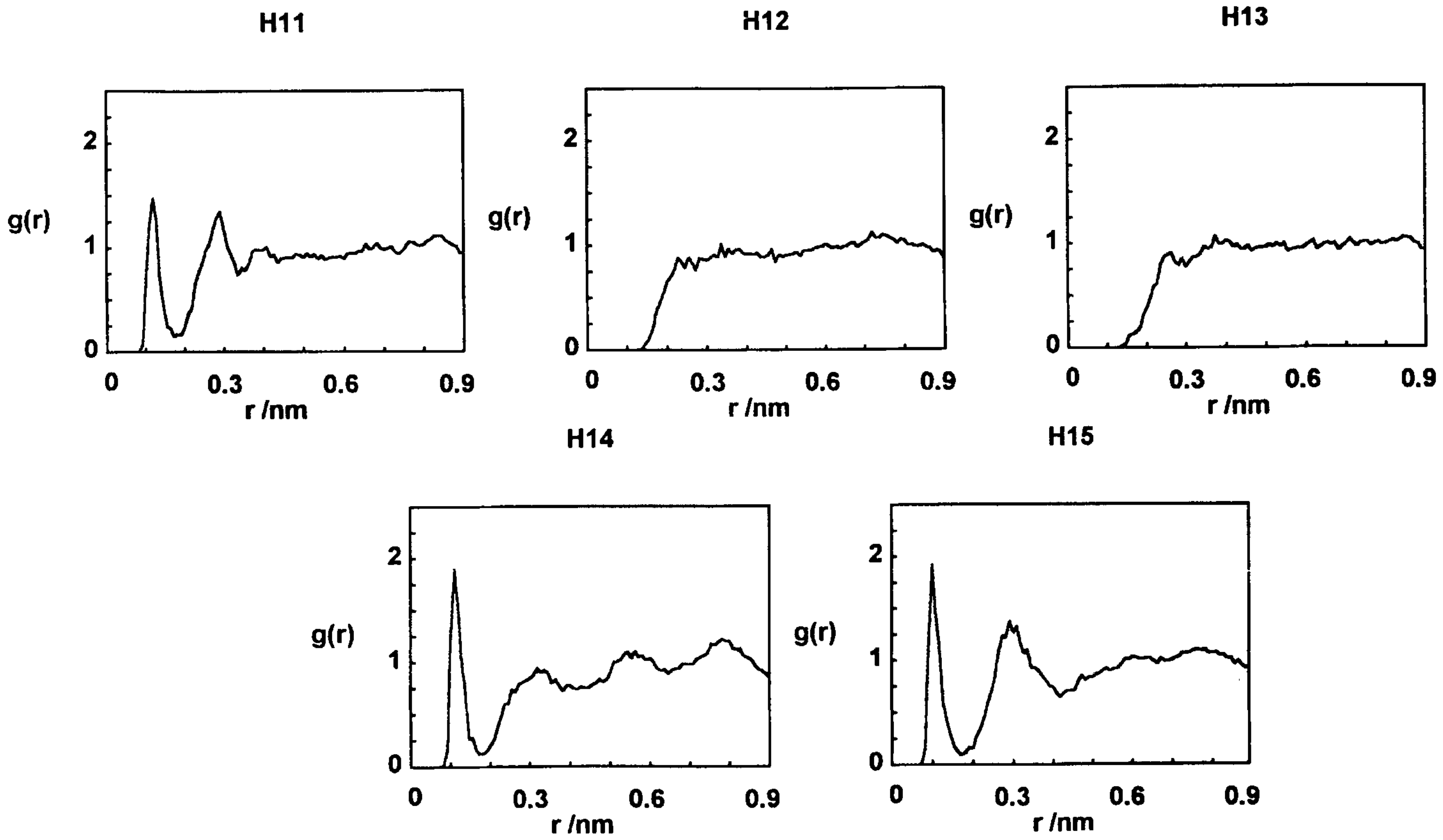

FIGURE 5 Computer radial distribution functions of water around hydrogen atoms of adenine.

The radial distribution function (RDF) of water around nitrogen atoms has similar general features for all charge sets. Figure 4 shows the RDF of water around nitrogen atoms. The only one that exhibits a clear hydrophilic character is the nitrogen N10, in which the first hydration shell is observed at 0.35 nm and the second at 0.35 nm. The other nitrogen atoms insinuates a slight first peak, which is what one would expect, without giving a clear hydration structure at its surroundings.

Regarding hydrogen atoms, H11 and H15 reveal polar trends, while H12 and H13 seem behave as non polar atoms. (Fig. 5). As H12 and H13 are part of the CH group they should not have polar properties. Although the explicit use of all protons [6,7] seem to be an advantage over the 'united atoms approach' some considerations have to be taking into account for the particular chemical bond between carbon and hydrogen atoms. Hydrogen atom H14 shows a well defined first peak but further peaks observed differs from the typical pattern of hydrophilic interaction. This situation also reflected in the RDF of the nitrogen atom N6 at which is attached (Fig. 4).

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4.4. The Hydrogen-Bond Network

The hydrogen bond networks give an additional information. The water-water hydrogen bonds for pure SPC/E water and the aqueous solution of

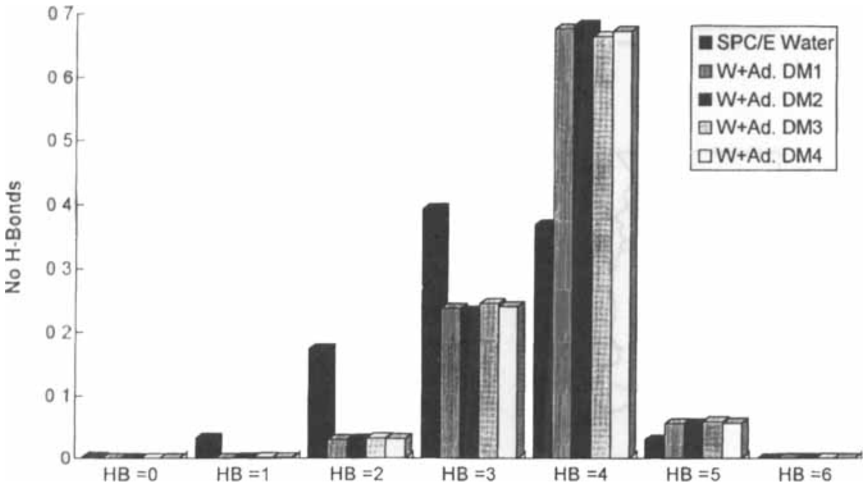

FIGURE 6 Distribution of hydrogen bonds in water for SPC/E water model and the solutions of adenine for the different charge sets studied.

adenine studied are shown comparatively in Figure 6 and Table II. The criteria for H-bond formation are the distance between the proton and acceptor ($d < 0.24$ nm) and the angle formed by the donor, hydrogen, and acceptor ($> 145°$). The number of hydrogen bonds are calculated over 100 ps and between zero and six hydrogen bonds are taken into account.

The average number of hydrogen bonds $\Delta \mathrm{N}^0$ is defined as

$$N^0 = \frac{\sum_{i=0}^{6} \mathrm{HB}i \times i}{\sum_{i=0}^{6} \mathrm{HB}i} = \sum_{i=0}^{6} \left(\frac{\mathrm{HB}i}{\sum_{i=0}^{6} \mathrm{HB}i} \right) \times i = \sum_{i=0}^{6} (\%\,\mathrm{hbonds}) \times i \qquad (2)$$

where HB = hydrogen bonds number, from $\mathrm{HB} = 0$ to $\mathrm{HB} = 6 (i = 0$ to $6)$

There is an increment of ΔN^0 for the adenine solution compared with pure water for all the partial charge sets used. We get for DM1, $\Delta N^0 = 3.756$, for DM2, $\Delta N^0 = 3.756$, for DM3, $\Delta N^0 = 3.744$ and for DM4, $\Delta N^0 = 3.749$. That gives and average value of $\Delta N^0 = 3.751$ (0.0006) which exceeds the value of $\Delta N^0 = 3.183$ computed for pure water.

Figure 6 shows the distribution of H bonds in water for SPC/E water and the solutions of adenine for all the charge sets under study. We see that the maximum shift for $\mathrm{HB} = 3$, for pure water, to $\mathrm{HB} = 4$ in the presence of adenine for all the charge sets studied. It seems that the presence of adenine maximizes the formation of four hydrogen bonds in water. This result is in agreement with the observed decrease of the water diffusion coefficient.

The increasing of hydrogen bonds of water reflects the overall hydrophobic behavior of the adenine. Recent simulation results [20] give further evidence about the increase of the ordering of water. This order may also extend to relative long distances [21, 22].

5. CONCLUSIONS

By analysis of the behavior of molecular simulations of an aqueous solution of adenine using for partial charges atoms sets we have been able to state

TABLE II Number of each type of hydrogen-bonds detected for water and adenine solutions for the different charge sets. The average (N^0) is defined in equation 2

H-bonds	*HB = 0*	*HB = 1*	*HB = 2*	*HB = 3*	*HB = 4*	*HB = 5*	*HB = 6*	N^0
W-W	2791	44447	234074	531405	496929	40106	248	3.183
A-Dm1	2	287	6235	49426	140579	11433	38	3.753
A-Dm2	2	280	6363	48411	141643	11273	28	3.756
A-Dm3	8	352	6678	50853	137970	12085	54	3.744
A-Dm4	3	289	6492	49955	139659	11564	38	3.749

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several aspects not only for the charge selection but also for the hydration characteristics of adenine.

In general we see that for adenine the molecular dynamics simulations are not very much sensitive to the method for which partial charges are obtained, at least for a single solute system like the one studied here. Whether or not the different charge set will influenciate the solute-solute interation we cannot decide form the present results.

As regards the interaction of adenine with water we can conclude that the presence of adenine modified strongly the hydrogen bonding pattern of the water as well as its dynamic properties producing an increasing of the for bounded water molecule and a slowing down in the diffusion coefficient. This effect of increasing the water association is a typical case of hydrophobic hydration. This result is consistent with the fact that DNA stability is strongly determined by hydrophobic interaction [23].

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Acknowledgements

This work has been partially supported by the Consejo Nacional de Investigaciones Cientificas y Tecnicas of Argentina (CONICET) and the Comision de Investigaciones Cientificas of the Province of Buenos Aires (CIC). J.M, A.F. and J.R.G.. are members of the Carrera del Investigador of CONICET and M.C.D is member of the Carrera del Investigador of CIC. E.I.H is fellow of CONICET.

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